

Remarks

Claims 5-6, 15-16 and 20-21 continue to stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Low in view of Connelly and further in view of Li. Specifically, the Examiner contends that the argument presented in the previous action, i.e. the fact that none of the cited prior art references in combination discloses the compounds of the invention containing a siRNA molecule, ignores the teachings of Li. According to the Examiner, Li discloses inhibitory dsRNAs “that are reasonably considered to be siRNAs according to the claimed invention.” While Applicants agree that Li discloses inhibitory dsRNAs, Applicants respectfully disagree that such dsRNAs can be “reasonably considered” siRNAs. In fact, Li teaches away from this notion.

Initially, the Supreme Court of the United States recently addressed the legal standard for determining obviousness under 35 U.S.C. § 103 in *KSR International. Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007).

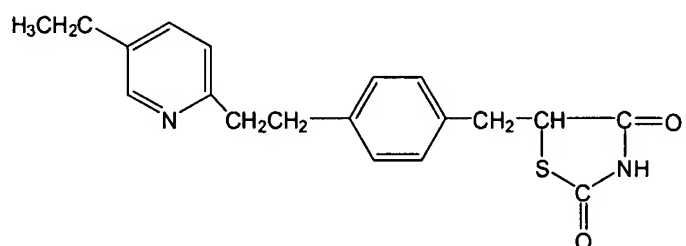
The *KSR* decision focused on how to determine obviousness when all elements of a claimed invention can be found in the prior art. Recognizing that “inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known,” (*KSR*, at 1741), the Supreme Court emphasized three factors: (1) whether there is an “apparent reason to combine the known elements in the fashion claimed by the patent at issue,” *id.* at 1740-41; (2) whether, when known elements are combined, there is predictability of yielding the claimed results; and (3) whether the prior art teaches away from modifying known elements in such a way that would lead to the claimed invention.

The Court found obviousness in *KSR* because “there is a design need or market pressure to solve a problem [*i.e.*, a reason] and there are *a finite number of identified, predictable* solutions.” *See id.*, at 1732 (*emphasis added*). The *KSR* Court emphasized the importance of using teaching-away references to guard against hindsight reconstruction, stating that “[w]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious.” *Id.* at 1740 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)). As such, teaching away is significant not only in undermining the reason(s) for making a claimed invention but also in diminishing the predictability of whether a combination of prior art elements may be successful. As discussed below, Low in view of Connelly and Li does just that, not only teaching away from making the claimed invention, but also suggesting the lack of predictability.

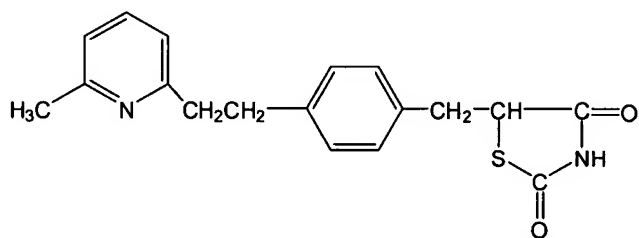
These factors have subsequently been interpreted by the Federal Circuit on several occasions. For example, applying the framework of *KSR* in *Pharmastem Therapeutics v. Viacell*, 83 U.S.P.Q.2d 1289, 1350 (Fed. Cir. 2007), the Federal Circuit held that (a) it is necessary to demonstrate that the prior art provides reasons to make the particular invention and not merely general guidance before finding obviousness and (b) “an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.” (quoting *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). Therefore, the mere fact that certain approaches can be undertaken

does not constitute a legally sufficient reason to combine the known elements in an obviousness inquiry.

Takeda Chemical Industries v. Alpharma, 2007 WL1839698, *15 (Fed. Cir. June 28, 2007), further illustrates the importance of having a finite number of identified, predictable solutions for a finding of obviousness. In *Takeda*, the claim at issue was directed to the compound pioglitazone, wherein an ethyl group is attached to the 5'-position of a pyridyl ring:



The alleged infringer argued that the claim at issue was obvious over the prior art compound b, which includes a pyridyl ring with a methyl group attached at the 6'-position:



The Federal Circuit agreed with the district court's finding of nonobviousness, despite the fact that the claimed compound differs from the alleged prior art compound in two seemingly minor aspects: (1) the type of substituent (methyl in compound b vs. ethyl in the claimed compound); and (2) the location of the substituent (at the 6-position on the pyridyl ring in compound b vs. at the 5-position in the claimed compound). The Federal Circuit found that the prior art would not have first led one of ordinary skill in the art to

select compound b as a lead compound for investigation, and then led that person to make two obvious chemical changes: replacing a methyl group with an ethyl group, and “ring-walk” the ethyl group to the 5’-position, despite the fact that compound b was disclosed in a prior art reference. The Federal Circuit called attention to the fact that the reference disclosed hundreds of millions of other compounds in the same family, and exemplified 54 of those compounds, including compound b, but was silent as to which of those compounds would have the desired properties. The Federal Circuit also found it important that another reference also disclosed compound b, but did not identify it as one of the three most favorable compounds, and in fact singled it out as one having prominent undesirable side effects. On these facts, the Federal Circuit approved the district court’s finding that a person of ordinary skill in the art would not have selected compound b as a lead compound.

The Federal Circuit then rejected the contention that, under *KSR*, it would have been obvious to pick compound b and modify it as claimed because the prior art compound fell within “the objective reach of the claim,” and the evidence demonstrated that using the techniques of homologation and ring-walking would have been “obvious to try.” According to the Federal Circuit, this was not a situation when there are a finite number of identified and predictable solutions to a problem. Instead, compound b “exhibited negative properties that would have directed one of ordinary skill in the art away from that compound.” *Id.* at *15. Thus, the Federal Circuit concluded, “this case fails to present the type of situation contemplated by the [*KSR*] Court when it stated that an invention may be deemed obvious if it was ‘obvious to try.’” *Id.*

The defendant's reliance on *Pfizer v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007) fared no better. Contrasting *Pfizer*, where obviousness was found because the prior art teaches how to narrow the possibilities of a large family of lead compounds to a group of efficacious ones, the Federal Circuit pointed to the district court's finding of nothing in the prior art to narrow the possibilities of millions of lead compounds to compound b in *Takeda*.

The Federal Circuit first analyzed the facts and reasoned that one of ordinary skill in the art would not have selected compound b from amongst the numerous compounds in the prior art for further study and modification. The Federal Circuit went on to state that even if the prior art would have led to the selection of compound b as the lead compound, the obviousness argument failed on a second ground. The Court found nothing in the prior art to suggest making the specific molecular modification to compound b that would lead to the claimed compounds. The Court also pointed out that studies have confirmed that several other compounds, "and one compound in particular, compound 99, that had no identified problems" in properties "differ significantly from compound b in structure." *Id.* at *18. The Court concluded that the process of modifying lead compounds was not routine at the time of the invention because of the great number of possible modifications, and because there was no way of predicting which of the modifications might bring about desired properties, especially in view of the fact that similar modifications did not always yield similar changes in properties. Therefore, there is no *prima facie* obviousness even when a general approach to a problem is known, if that general approach yields numerous choices, and the prior art does not help to predict which of those choices would be efficacious.

Takeda also illustrates how a prior art reference teaching away from the claimed invention may further buttress the want of predictability. Specifically, evidence in the prior art that certain modifications produce undesirable properties should be taken as not only leading a skilled artisan away from those particular modifications, but also as suggesting the lack of predictability on how similar modifications may fare. In other words, if the prior art teaches that certain modifications sometimes but not always give rise to the desired properties, there is no way of predicting what other similar modifications may do.

Applying the post-*KSR* framework, Applicants submit that, at the time of the present invention, a skilled artisan would not have modified the compounds in Low in view of Connolly by attaching the dsRNA in Li, because potentially millions, if not more, prospective chemical compounds could have been generated by combining a biologically active molecule conjugated to a cluster of three substituted N-acetylgalactosamine residues and attached with various dsRNAs. The cited references are either silent as to which of the modified molecules might be efficacious, or teach away from making certain of the modifications. Thus, the problem faced by the instant applicants at the time of this invention did not have a “finite number of identified, predictable solutions,” and the instant claims are accordingly not *prima facie* obvious.

The Examiner alleges that Li “discloses and enables inhibitory dsRNAs that are reasonably considered to be siRNAs according to the invention.” According to the invention, double stranded siRNA molecules are about 19 to 25 nucleotides in length and single stranded siRNA molecules are about 38-50 nucleotides in length (See page 92, line 34 to page 93, line 4). Li, at page 12 starting with line 26, discloses that its double

stranded RNAs be at least 25 bases in length, preferably at least about 50 bases in length, and most preferably at least from between 100-200 bases in length. Thus, in fact, Li is teaching away from introducing dsRNAs 25 bases or less in length into cells, etc. to attenuate gene expression.

Along similar lines, the Examiner alleges that Low “discloses that a wide variety of different single and double stranded nucleic acids of various lengths...can all be enhanced in their transmembrane transport by being conjugated to a molecule that is naturally taken up into a cell.” Low does not provide the reason to modify a siRNA molecule in the manner recited in the instant claims. It is completely silent to siRNA molecules, in general. Merely stating that certain molecules can be improved upon or identified does not provide the requisite reason or predictably for making the improved or identified compounds. It has been established that, “in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a *particular* manner to establish prima facie obviousness of a new claimed compound.” *Takeda*, at *10 (emphasis added). Low, alone or in combination with Connolly and Li, does not provide a reason to conjugate a *siRNA molecule* for enhanced transmembrane transport.

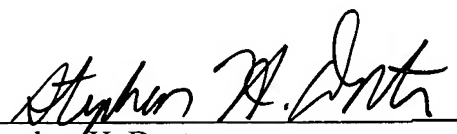
Even if Low were correctly combined with Connolly or Li, the combination of references would still not arrive at the claimed invention, since the teachings of Li would lead one skilled in the art to afford conjugates comprising a dsRNA of length between 100-200 nucleotides conjugated to a cluster of three N-acetylgalactosamine residues via a trivalent linker. The combination of references, therefore, does not teach each and every element of the instant claims. Accordingly, even if Low could be taken as prior art,

it does not alone, or in combination with the other cited references, render the instant claims obvious. Withdrawal of the obviousness rejection is therefore respectfully requested.

Allowance of the claims and passage of the case to issue is respectfully solicited. Should the Examiner believe a discussion of this matter would be helpful, he is invited to telephone the undersigned at (312) 913-0001.

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